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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/805,813	02/26/1997	ICHIRO MITSUHARA	085760-000	2736

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EXAMINER
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ART UNIT	PAPER NUMBER
1638	42

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/805,813	Applicant(s) MITSUHARA ET AL.	
	Examiner Anne Kubelik	Art Unit 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03-18-02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The request filed on 18 March, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/805,813 is acceptable and a CPA has been established. An action on the CPA follows.

2. The cancellation of claims 21-47 and the addition of new claims 48-67 requested in Paper No. 41, filed 18 March, 2002, have been entered. Claims 48-67 are pending.

Claim Objections

3. Claim 49 is objected to because "*and*" in line 2 should not be italicized.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 48-67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Neither the instant specification nor the originally filed claims appear to provide support for the phrases "sarcotoxin 1 family", "cecropin family" or "cecropin A". Thus, such phrases constitute NEW MATTER. In response to this rejection, Applicant is required to point to support for the phrases or to cancel the new matter.

6. Claims 48-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of conferring on a plant resistance to pathogenic fungi by transformation with an expression cassette encoding a fusion protein comprising the PR-1a signal peptide, sarcotoxin 1a, the hinge region of tobacco chitinase and the mature PR-1a operably linked to a dual promoter comprising an inducible promoter and a constitutive promoter, and plants so transformed, does not reasonably provide enablement for a method of conferring on a plant resistance to pathogenic fungi by transformation with an expression cassette encoding a cecropin or any sarcotoxin 1 protein operably linked to a dual promoter comprising an inducible promoter and a constitutive promoter, and plants so transformed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to a method of conferring on a plant resistance to pathogenic fungi by transformation with an expression cassette encoding a cecropin or sarcotoxin 1 protein operably linked to a dual promoter comprising an inducible promoter and a constitutive promoter, and plants so transformed.

The instant specification, however, only provides guidance for construction of an expression cassette comprising the PR-1a promoter, a sequence encoding the PR-1a signal peptide, a sequence encoding the HMPR-1a fragment (the hinge region of tobacco chitinase and a region encoding the mature PR-1a), a sequence encoding the mature form of sarcotoxin 1a, and the Pr-1a terminator (example 1), insertion of that cassette into a plant expression vector so that the CaMV 35S promoter driving expression of the marker gene is located directly upstream of

the expression cassette (example 2), *Agrobacterium*-mediated transformation of the vector or a vector encoding a non-fusion sarcotoxin into tobacco (example 3), detection of the sarcotoxin protein in transformed plants by western blotting (example 4), analysis of the resistance of the transformed plants to *Pseudomonas syringae* pv. *tabaci* (example 5) and *Erwinia carotovora* subsp. *carotovora* (example 6), measurement of the *in vitro* antifungal activity of sarcotoxin 1a against *Fusarium oxysporum* F-3, *Rhizoctonia solani*, and *R. solani* AG-4 1272 (example 7), and analysis of the resistance of the transformed plants to *R. solani* (example 8), *Pythium aphanidermatum* (example 9), and *Phytophthora infestans* (example 10).

The instant specification fails to provide guidance for nucleic acids encoding cecropin family proteins or for nucleic acids encoding sarcotoxin 1 proteins other than sarcotoxin 1a. The instant specification also fails to provide guidance for a method of conferring on a plant resistance to pathogenic fungi by transformation with an expression cassette encoding a cecropin or sarcotoxin 1 protein operably linked to a dual promoter comprising an inducible promoter and a constitutive promoter where the antibacterial peptide is not part of a fusion protein with PR-1a.

The instant specification states on pg 2, lines 18-22:

> since a short peptide such as Sarcotoxin 1a is expected to be unstable in plants, it is necessary to stabilize the peptide by producing it as a fusion protein with PR-1a which is an [*sic*] pathogenesis related protein of tobacco.

The specification reiterates the requirement on pg 16, lines 13-17. However, the claims are not drawn to methods of conferring resistance by transformation with such fusion constructs.

Expressing cecropins in plants is unpredictable. The cecropin CEMA is toxic to plants, and requires modification of the N-terminus to reduce toxicity to plants while retaining toxicity to pathogens (Osusky et al, 2000, Nature Biotechnol. 18:1162-1166; see pg 1162, last paragraph, to pg 1163, 1st paragraph, and pg 1165). Cavallarin et al (1998, Mol. Plant Microbe

Interact. 11:218-227) review the many examples of plants that were transformed with a cecropin gene but displayed no increase in pathogen resistance, and state that the precise structural changes required in cecropin sequences are crop-specific (paragraph spanning pg 218-219). The instant specification does not teach all these modifications of cecropin structure required for functioning in plants.

Transformation with a sarcotoxin 1a gene is also unpredictable. Okamoto et al (1998, Plant Cell Physiol. 39:57-63) transformed tobacco with 4 different constructs encoding sarcotoxin 1a fused to a GUS gene, in either order, and with and without a signal peptide; the phenotypes of plants transformed with 3 of these 4 constructs were unexpectedly not normal and the disease resistance in those plants was reduced (paragraph spanning pg 60-61, and pg 61, right column, paragraph 2).

The specification also fails to provide guidance for the selection of the promoter induced by stress. The specification states the promoter "is induced by a certain kind of stress" (pg 9, line 8), but other than mentioning the PP-1a promoter provides no guidance for what kind of stress is intended or what other promoters are suitable.

As the specification does not describe the transformation of any plant with a cecropin family gene or with a sarcotoxin 1 family gene other than sarcotoxin 1a linked to a PR-1a signal peptide and the HMPR-1a fragment or using any inducible promoter other than the PR-1a promoter, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with increased resistance to pathogenic fungi, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

Applicant's arguments filed 18 March, 2002, in response to similar rejection in the Office action mailed 9 March, 2001, have been fully considered but they are not persuasive.

Applicant urges that many nucleic acids encoding sarcotoxin 1 and cecropin family peptides were published prior to the priority date of the instant application and that sarcotoxins and cecropins were well characterized. Applicant also cites references published after the priority date of the instant application that state that cecropin A and B have fungicidal activity. Applicant urges that unlike Florack et al, cited in a prior Office action, the instant specification teaches a dual promoter system for expression of sarcotoxin or cecropin (response pg 9-13).

This is not found persuasive because the instant specification fails to teach a method of conferring on a plant resistance to pathogenic fungi by transformation with an expression cassette encoding a sarcotoxin 1 and cecropin family peptides other than sarcotoxin 1a as part of a fusion protein and under control of the dual promoter. The instant specification also fails to teach that nucleic acids encoding other sarcotoxin 1 family peptides or that cecropin family peptides could be used in the instant method.

7. Claims 48-49, 51-59 and 61-67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

No description is provided as to the structural features of all nucleic acids that encode a cecropin protein or a sarcotoxin 1 other than sarcotoxin 1a. The instant specification fails to describe the sequences of the nucleic acids encoding any cecropin, including the mosquito cecropins (*e.g.*, Sun et al, 1999, FEBS Lett: 454:147-151), and fails to describe any nucleic acid encoding a sarcotoxin other than sarcotoxin 1a. Thus, plants transformed with those nucleic acids and methods of using those nucleic acids have not been described.

Hence, Applicant has not, in fact, described nucleic acids encoding all sarcotoxin 1 or cecropin proteins, plants transformed with those nucleic acids and methods of using those nucleic acid within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

See *Uni. of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997):

> The name cDNA is not in itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA .... Accordingly, the specification does not provide a written description of the invention ....

and at pg 1406:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicted, does not suffice to define the genus because it is only an indication of what the genes does, not what it is.

See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016 at page 1021:

> A gene is a chemical compound, albeit a complex one, and ... conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials .... Conception does not occur unless one has a mental picture of the structure of the chemical or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by it principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.

Applicant's arguments filed 18 March, 2002, in response to a similar rejection in the Office action mailed 9 March, 2001, have been fully considered but they are not persuasive.

Applicant urges that the claimed invention is not the identification of genes encoding antibacterial peptides from Diptera, but is a method of using such genes and plants thereby produced. Applicant has amended the claims to limit them to use of nucleic acids encoding sarcotoxin 1 and cecropin family peptides, the sequences of many of which were published prior to the priority date of the instant application. (response pg 6-9).

This is not found persuasive because the claims are broadly drawn to methods of conferring resistance to pathogenic fungi by transformation with any nucleic acid encoding a sarcotoxin 1 or cecropin protein, and plants so transformed.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 48-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections.

In claim 48, lines 2-3, it is unclear what the phrase "using a DNA .... Diptera insect" is intended to modify. It is also unclear how the DNA sequence is used. It is suggested that the phrase be deleted.

In claim 48, line 4, it is unclear to what the DNA sequence is introduced.

Claim 48 lacks antecedent basis for the limitation "the transformed plant" in line 5 and "the DNA" in line 7.

It is unclear where in the expression vector used in the method of claim 48 the DNA sequence encoding the sacrotoxin 1 or cecropin family member is positioned relative to the promoters.

Similarly, it is unclear in the method of claim 52 if the expression cassette further comprises parts (i) and (ii) or if parts (i) and (ii) are intended to further limit the expression cassette used in the method of claim 48.

In claims 53 and 62, it is unclear if the hinge region of a tobacco chitinase gene is part of the expression cassette and where and how it is positioned relative to the other components of the cassette.

Similarly, in claims 54 and 63, it is not clear where the signal sequence is located. Also, it is not clear of the gene itself acts as a signal sequence or if a nucleic acid encoding a signal sequence is operably linked to the DNA sequence.

It is unclear in claim 58 on what the plant confers resistance to pathogenic fungi.

In claim 67, it is not clear if the drug resistance gene is the same as the drug resistance gene in part (ii) of claim 58 and where this second drug resistance gene or second copy of the drug resistance gene is located in the expression vector.

10. Claims 48-67 are free of the prior art, given the failure of the prior art to teach or suggest a method of conferring on a plant resistance to pathogenic fungi by transformation with an

expression cassette encoding a cecropin or sarcotoxin 1 protein operably linked to a dual promoter comprising an inducible promoter and a constitutive promoter, and plants thereby obtained.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kimberly Davis, at (703) 305-3015.

Anne R. Kubelik, Ph.D.
May 31, 2002

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